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One-Year Comparative Effectiveness of Ustekinumab Versus Tofacitinib for Ulcerative Colitis After Anti-Tumor Necrosis Factor Failure

Rahul S. Dalal[1], MD, MPH, Puza P. Sharma[2], MD, PhD, Kanwal Bains[3], MBBS, Jordan C. Pruce[1], BS, Jessica R. Allegretti[1], MD, MPH

[1] Division of Gastroenterology, Hepatology and Endoscopy, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

[2]Pfizer Inc, New York, NY, USA

[3]Department of Nutrition, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA

Background and Rationale

- Clinical trials have demonstrated the efficacy of induction and maintenance tofacitinib and ustekinumab compared to placebo in patients with ulcerative colitis (UC).[1,2]
- There are no head to head trails comparing Ustekinumab vs. Tofacitinib. However, a recent meta-analysis equally positions both of these agents after anti-tumor necrosis factor agents (anti-TNFs).[3]
- A recent, real-world comparative effectiveness analysis among patients with both anti-TNF and vedolizumab failure found no difference in steroid-free remission rates between tofacitinib and ustekinumab at 12-16 weeks.[4]
- We sought to compare real-world outcomes of tofacitinib vs ustekinumab up to 52 weeks after drug initiation among UC patients with anti-TNF failure.

1. Sandborn WJ et al. *N Engl J Med*. 05 2017;376(18):1723-1736..
2. Sands BE et al. N Engl J Med. 2019 Sep 26;381(13):1201-1214.
3. Singh S et al. Clin Gastroenterol Hepatol. 2020 Sep;18(10):2179-2191
4. Dalal RS et al. Inflamm Bowel Dis. 2021 Oct 18;27(10):1694-1697.

Methods

Design: Retrospective cohort study

Population: Adults with UC and ≥1 prior anti-TNF failure who initiated tofacitinib or ustekinumab May 1, 2018 - April 1, 2021

Setting: The Mass General Brigham health system (Boston, MA).

Primary endpoints: Proportion of patients in steroid-free clinical remission at 12 weeks and 52 weeks (i.e. SFCR 12 and SFCR 52). +/- 4 weeks were allowed to account for variability in timing of real-world assessments.

Secondary endpoints: Drug survival, endoscopic response/remission, biochemical response/remission, improvement in arthralgia, hospitalization, colectomy, adverse events requiring discontinuation, drug discontinuation within 52 weeks.

Analysis: Inverse probability of treatment-weighted (IPTW) logistic and Cox regression. Covariate balance confirmed with <|10%| standardized differences. Kaplan-Meier analysis with log-rank test were used to compare drug survival.

Results: Baseline Patient Characteristics

Baseline Characteristic	Ustekinumab (n=97)	Tofacitinib (n=69)	P-value*
Female	49 (51%)	42 (61%)	0.19
Age, y, median (IQR)	35.5 (29.4-50.4)	41.2 (28.1-54.0)	0.25
UC duration, y, median (IQR)	9.0 (4.1-13.5)	9.5 (4.4-15.5)	0.39
Race			
Caucasian	85 (88%)	63 (91%)	0.40
Black	4 (4%)	0 (0%)	
Asian	5 (5%)	4 (6%)	
Other/Unknown	3 (3%)	2 (3%)	
Ethnicity			
Non-Hispanic	89 (92%)	69 (100%)	0.05
Hispanic	4 (4%)	0 (0%)	
Unknown	4 (4%)	0 (0%)	
Malignancy history	5 (5%)	4 (6%)	0.86
Number of prior anti-TNFs, median (IQR)	1 (1-2)	2 (1-2)	0.18
Prior vedolizumab	64 (66%)	51 (74%)	0.27
Prior 5-ASA	94 (97%)	67 (97%)	0.94
Current 5-ASA	19 (20%)	10 (14%)	0.39
Prior immunomodulator	70 (72%)	54 (78%)	0.37
Current immunomodulator	**24 (25%)**	**6 (9%)**	**0.008**
Current Oral/IV corticosteroids			0.41
Prednisone/Methylprednisolone	51 (53%)	30 (43%)	
Budesonide	11 (11%)	7 (10%)	

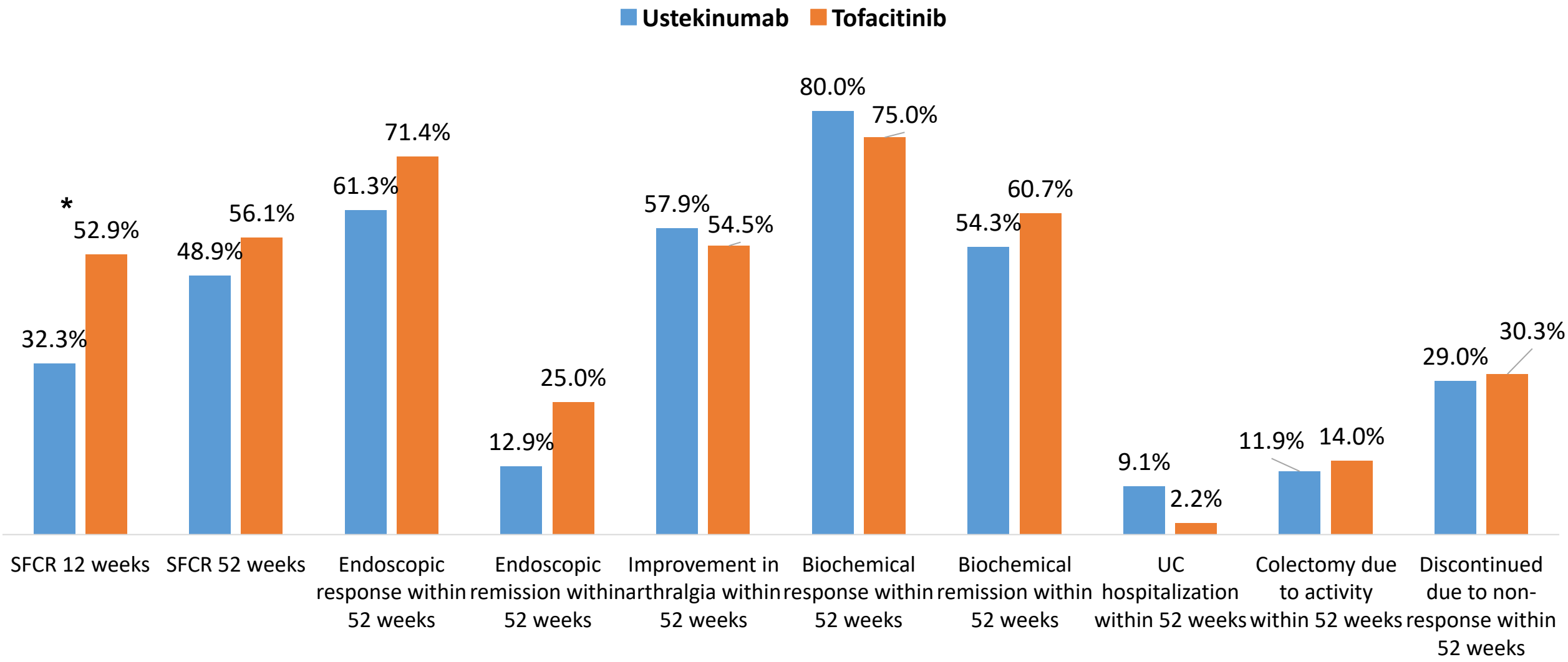
*Calculated using Fisher's exact test or Wilcoxon rank sum test

Results: Baseline Patient Characteristics (cont.)

Baseline Characteristic	Ustekinumab (n=97)	Tofacitinib (n=69)	P-value*
BMI, kg/m^2, median (IQR)	25.1 (21.7-29.0)	25.79 (21.8-28.9)	0.97
Arthralgia	26 (27%)	26 (38%)	0.14
Montreal disease extent >E1 (i.e. >proctitis)	75 (77%)	59 (86%)	0.19
Mayo endoscopic subscore (severity)			**0.049**
0 (None)	**10 (10%)**	**6 (9%)**	
1 (Mild)	**20 (21%)**	**7 (10%)**	
2 (Moderate)	**32 (33%)**	**37 (54%)**	
3 (Severe)	**35 (36%)**	**19 (28%)**	
Smoking			0.31
Never	70 (72%)	56 (81%)	
Current	2 (2%)	2 (3%)	
Former	25 (26%)	11 (16%)	
Current cannabis use	22 (23%)	9 (13%)	0.12
Current opioid use	3 (3%)	6 (9%)	0.12
UC hospitalization within 12 months	21 (22%)	18 (26%)	0.51
Serum albumin, g/dL, median (IQR)	4.1 (3.8-4.4)	4.1 (3.8-4.3)	0.47
C-reactive protein, mg/L, median (IQR)	**2.8 (1-7)**	**5.1 (1.8-22.8)**	**0.01**
Fecal calprotectin > 120 ug/g	49 (88%)	25 (89%)	0.81
SCCAI, median (IQR)	5 (3-7)	5 (4-8)	0.46
Daily bowel movement frequency, median (IQR)	6 (4-9)	6 (4-10)	0.57

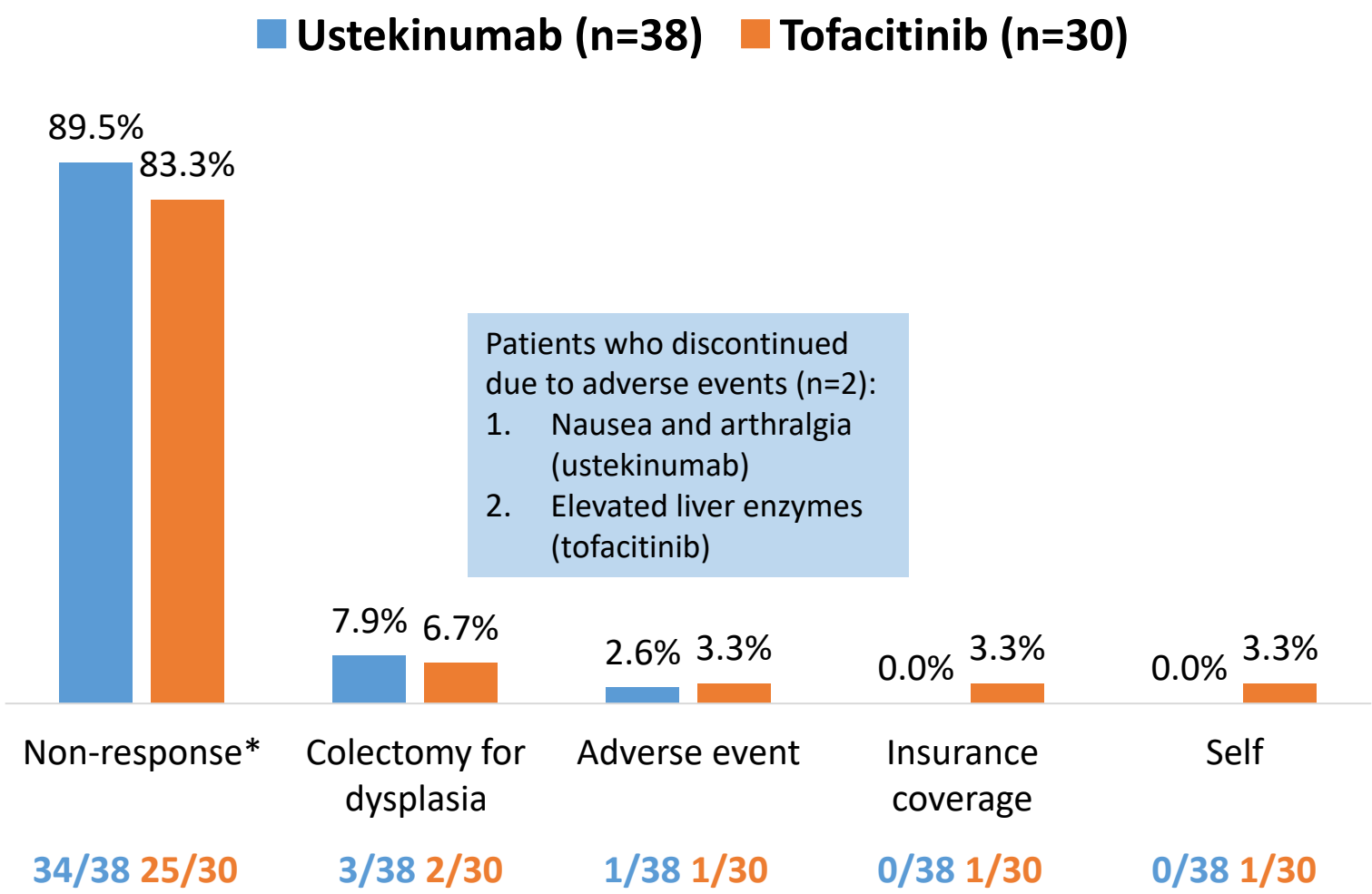
*Calculated using Fisher's exact test or Wilcoxon rank sum test

Results: Outcomes



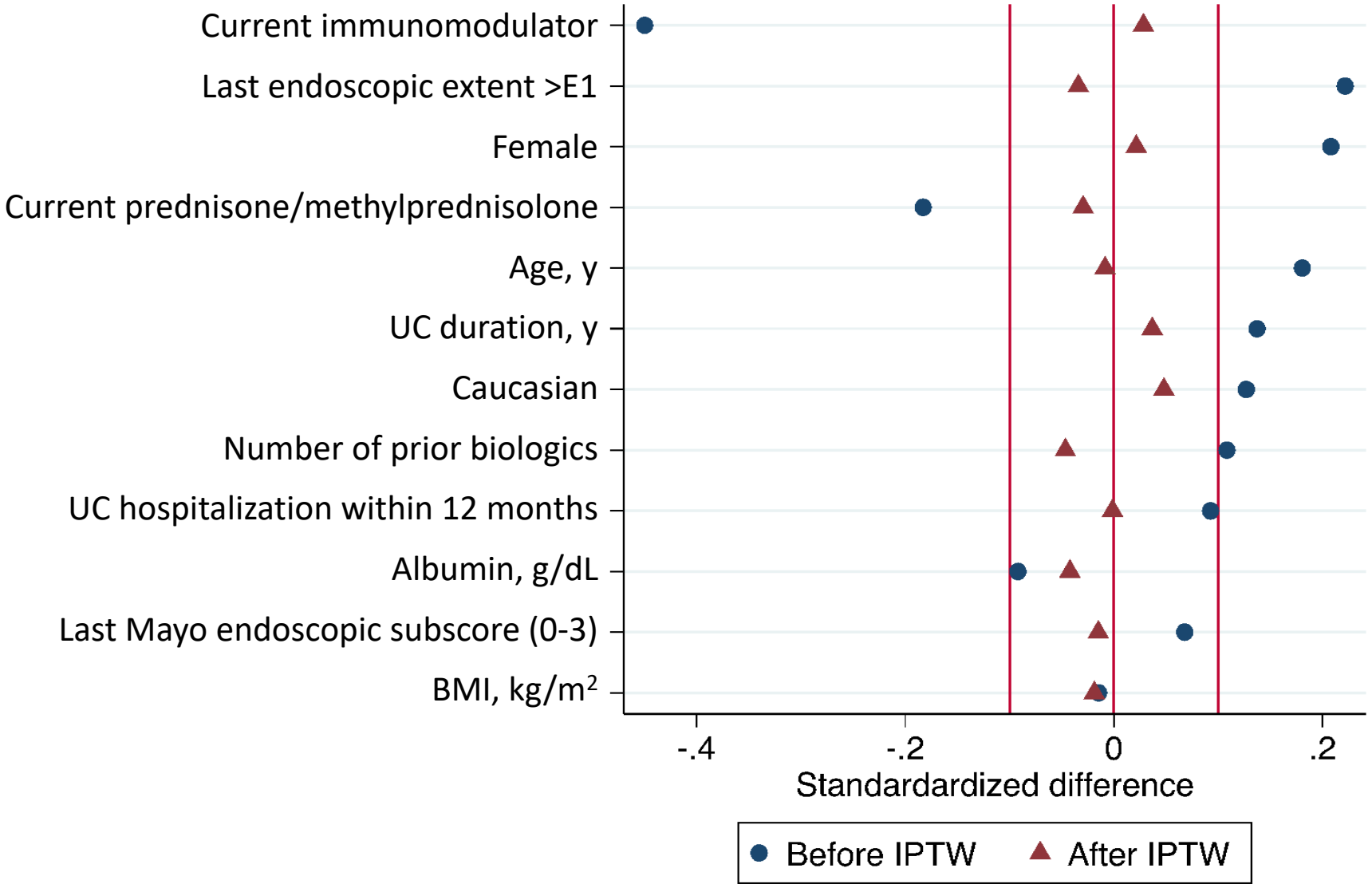
*p<0.05

Results: Reasons for Drug Discontinuation



*Includes colectomy for refractory disease

Results: Covariate Balance Before and After IPTW

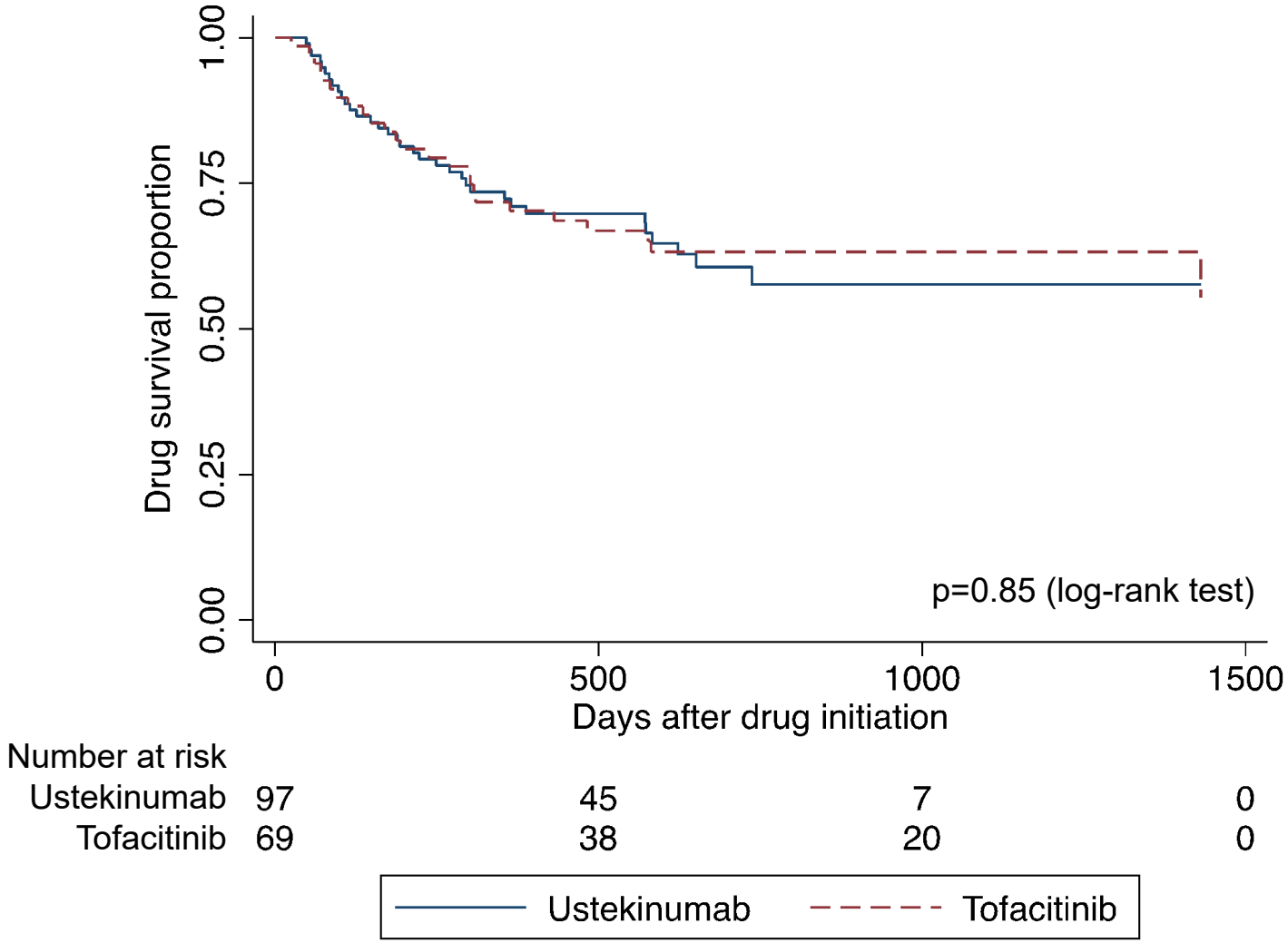


Results: IPTW Logistic Regression

SFCR 12	OR	P-value	95% LCL	95% UCL
Tofacitinib vs Ustekinumab	1.94	0.064	0.96	3.92
SFCR 52	**OR**	**P-value**	**95% LCL**	**95% UCL**
Tofacitinib vs Ustekinumab	1.16	0.681	0.58	2.31

Abbreviations: OR = odds ratio, LCL = lower confidence limit, UCL = upper confidence limit

Results: Drug Survival



IPTW Cox Model	HR	P-value	95% LCL	95% UCL
Tofacitinib vs Ustekinumab	1.26	0.399	0.74	2.15

Abbreviations: HR = hazard ratio, LCL = lower confidence limit, UCL = upper confidence limit

Summary and Conclusions

- Compared to ustekinumab, tofacitinib-treated patients had higher baseline CRP and more commonly had a Mayo endoscopic subscore ≥2.
- Ustekinumab and tofacitinib were both effective in achieving SFCR at 52 weeks (>45% for both groups).
- After adjustment for confounding, there were no significant differences in SFCR at 12 or 52 weeks or drug survival between tofacitinib and ustekinumab.
- Adverse events leading to treatment discontinuation were rare.
- Strengths: Granular data regarding drug discontinuation and endoscopic/biochemical response, successful balance of confounding variables with IPTW
- Limitations: Retrospective design, incomplete data, variable follow-up time, unmeasured confounding, limited power to detect small differences in outcomes
- Further study: Large, prospective real-world studies are needed to confirm these findings.

Thank you! Questions?

@RahulSDalalMD

@DrJessicaA

@AllegrettiLab

@BrighamGI

Additional/optional slides for Q&A

Sensitivity analysis with CRP added to IPTW logistic regression models

SFCR 12	OR	P-value	95% LCL	95% UCL
Tofacitinib vs Ustekinumab	1.61	0.196	0.78	3.34
CRP	1.00	0.870	0.98	1.01
SFCR 52	**OR**	**P-value**	**95% LCL**	**95% UCL**
Tofacitinib vs Ustekinumab	1.08	0.845	0.52	2.23
CRP	1.00	0.790	0.98	1.01

Sensitivity analysis with CRP added to IPTW Cox model

Cox	HR	P-value	95% LCL	95% UCL
Tofacitinib vs Ustekinumab	1.30	0.335	0.76	2.24
CRP	1.00	0.777	0.98	1.01